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INVITED REVIEW

Prostate Cancer

Radium-223 in metastatic castration resistant prostate cancer

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In 2004, docetaxel was approved for the treatment of metastatic castration-resistant prostate cancer (mCRPC). For the next several years, there was a lull in drug approvals. However, from 2010 onwards, 5 additional therapies have been approved on the basis of showing a survival benefit in phase III studies. These agents include sipuleucel-T, cabazitaxel, abiraterone, enzalutamide and (most recently) radium-223. Amongst radiopharmaceuticals currently used for advanced prostate cancer (e.g. samarium-153 and strontium-89), radium-223 possesses several unique properties. As an alpha-emitting compound, the agent produces a high-energy output over a short range, facilitating selective destruction of tissue within the bone in the region of osteoblastic lesions while sparing surrounding normal tissue. The current review will outline biological rationale for radium-223 and also provide an overview of preclinical and clinical development of the agent. Rational sequencing of radium-223 and combinations, in the increasingly complex landscape of mCRPC will be discussed, along with factors influencing clinical implementation.

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INTRODUCTION

Prostate cancer represents the most commonly diagnosed solid tumor in men, with an anticipated 238,590 diagnoses in 2013.¹ Although, the majority of patients are diagnosed with localized disease, a substantial proportion of patients will ultimately develop metastases. Metastatic prostate cancer has frequently been dichotomized in 2 distinct disease states. In the setting of castration-sensitive disease, patients respond to androgen deprivation therapies typically given as luteinizing hormone releasing hormone agonists or antagonists, alone or in combination with first-generation antiandrogens (e.g. bicalutamide, nilutamide or flutamide).² By a variety of mechanisms, castration-resistant disease ultimately develops. Metastatic castration-resistant prostate cancer (mCRPC) was historically characterized by a barren treatment landscape. The approval of docetaxel in 2004 was a breakthrough, marking the first agent for mCRPC to demonstrate an improvement in overall survival (OS) in phase III studies.^{3–5}

Since that time, the treatment landscape for mCRPC has evolved rapidly. The agent cabazitaxel, a taxane structurally similar to docetaxel, was shown to improve OS relative to mitoxantrone in a phase III trial.^{6,7} Outside of cytotoxic therapies, three new classes of agents have been Food and Drug Administration (FDA) approved and incorporated in mCRPC treatment algorithms on the basis of phase III studies showing an improvement in OS: (1) cancer vaccines, (2) novel endocrine therapies and (3) radiopharmaceuticals. Sipuleucel-T, an autologous dendritic cell vaccine, falls in the first category.⁸ In the phase III IMPACT trial, sipuleucel-T was shown to yield an improvement in OS relative to non-vaccinated cells in patients with asymptomatic or minimally symptomatic mCRPC.⁹ Abiraterone and enzalutamide

constitute the currently approved novel endocrine therapies. Abiraterone was initially approved in the post-docetaxel setting on the basis of the phase III COU-AA-301 trial – more recently, a second phase III study (COU-AA-302) has led to a further approval for use in chemotherapy-naïve patients.^{10–12} Enzalutamide has followed a similar trajectory – while initially approved in the post-chemotherapy space based on the phase III AFFIRM trial, a press release from the phase III PREVAIL trial suggests that the agent may be useful in prolonging survival in the pre-chemotherapy space as well.^{13–15}

The last category of newly approved therapies, radiopharmaceuticals, has a long and complex history in the management of advanced prostate cancer. Agents such as samarium-153 and strontium-89 have been used for palliative purposes, but do not provide a survival advantage.^{16–18} The current review will focus primarily on radium-223. Radium-223 (Xofigo) was approved on May 15, 2013 by the US FDA on the basis of the phase III ASLYMPCA study.^{19,20} Herein, both preclinical and clinical development of radium-223 will be outlined, with discussion of how this agent may be used in an evolving landscape of therapies for mCRPC.

BIOLOGY AND RATIONALE FOR RADIUM-223

Certain radiopharmaceuticals (e.g. strontium-89 and radium-223) are termed alkali earth metal as they fall into the second column of the periodic table – each of these compounds bind to hydroxyapatite.²¹ Other agents, such as samarium-153 and rhenium-186, require carriers that facilitate hydroxyapatite binding. All of these agents tend to preferentially incorporate in osteoblastic bone as compared to normal bone. The activity of radiopharmaceuticals is predicated on decay and

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subsequent release of high-energy particles. Several existing agents are beta-emitters, with release of electrons during the course of decay.²² Agents falling in this category include strontium-89, samarium-153 and phosphorous-32. Gamma-emitting drugs can be used for imaging such as rhenium-186 and samarium-153.²³ Radium-223 distinguishes itself from other agents as an alpha-emitter (**Figure 1**).

The release of alpha particles (when compared with beta or gamma) has theoretical advantages.²² First, linear energy transfer (LET) tends to vary among these agents – alpha particles have high LET, whereas beta and gamma particles have low LET. For example, the range of ionizing radiation of beta and gamma particles is typically between 1 and 10 mm within bone.²¹ The range of strontium-89 is approximately 8 mm and the range of samarium-153 is roughly 3 mm. In contrast, alpha particles have a very short range of activity, typically < 0.1 mm. By virtue of this, alpha-emitters have less penetration of surrounding normal tissue when incorporating in diseased bone. Clinically, this manifests with a reduced degree of myelosuppression with these agents. The oxygen enhancement ratio (OER) also varies. The OER provides a relative assessment of the energy needed to induce cytotoxicity in hypoxic cells relative to normoxic cells. While, this ratio is 2–3 for beta-emitting agents, this ratio is lower (approximately 1) for alpha-emitters.²¹

PRECLINICAL DATA

The compelling biologic rationale for alpha-emitters fueled further examination of radium-223 in preclinical models. Henriksen *et al.*²⁴ in their study have reported the activity of the compound in MT-1 rodent xenografts, a model of skeletal metastasis. Biodistribution studies in this model identified selective uptake of the compound in bone when compared to soft-tissue. Over the course of time, the relative content of radium-223 in non-bone metastatic sites (including liver, spleen and kidney) increased relative to content in the femur. All control animals (receiving no therapy) were sacrificed between 20 and 30 days secondary to paralysis caused by spinal infiltration of tumor. In contrast, mice receiving radium-223 developed symptoms significantly later and many (7 of 19, or 37%) were alive beyond 67 days. Furthermore, examination of the bone marrow of sacrificed animals showed no significant changes with radium-223. In a separate report, Henriksen *et al.*²⁵ performed a direct comparison of the biodistribution of radium-223 with strontium-89 in murine xenograft models. Both compounds were found in a higher concentration at bony surfaces as compared to soft-tissues. Distribution at soft-tissue sites was limited with both compounds. Supporting the notion that beta-emitters may be more myelotoxic than alpha-emitters, radium-223 was estimated to cause less damage to normal marrow when compared with strontium-89 based on dose deposition.

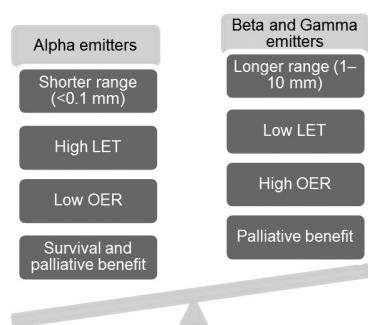


Figure 1: Advantageous properties of alpha-emitting compounds relative to beta- and gamma-emitters (LET: linear energy transfer; OER: oxygen enhancement ratio).

Phase I assessment

Nilsson *et al.*²⁶ in their study have reported the first clinical experience with radium-223. In a phase I study exploring 5 dose levels of the compound (46, 93, 163, 213 and 250 kBq kg⁻¹), a total of 15 prostate cancer patients and 10 breast cancer patients were enrolled. At each dose level, five patients received a single dose of drug with evaluation of pain response at weeks 1, 4 and 8. Improvements in pain were noted in 50%–60% of patients at each of the consecutive time points. A median OS of roughly 20 months was noted and declines in alkaline phosphatase (ALP) levels were noted in 29% and 52% of breast and prostate cancer patients, respectively. Toxicities were generally mild, even at the highest dose levels explored. The incidence of grade 3 neutropenia was only 12%. Notably, imaging studies accompanying this phase I effort suggested that the majority of radium-223 accumulated in metastatic bone lesions.

A second phase I study reported by Carrasquillo *et al.*²⁷ assessed a total of 10 patients with mCRPC. A different array of dose levels of radium-223 when compared with the aforementioned experience was explored (50, 100 and 200 kBq kg⁻¹). All patients received a single-dose of the agent, while 6 patients (60%) received a second dose of radium-223 at 50 kBq kg⁻¹. In this small cohort of patients, no dose-limiting toxicities were observed. Radium-223 was rapidly cleared from circulation, with pharmacokinetic studies suggesting only 0.5% of the drug remaining in the vasculature 24 h after administration. The majority of excretion occurred through a fecal route – at 24 h, 52% of administered radium-223 was detected in the gastrointestinal tract. As in the previously noted phase I experience, the majority of toxicities were hematologic, with 60%, 70% and 30% of patients developing all grade anemia, leukopenia and thrombocytopenia, respectively. Grade 3/4 leukopenia was observed in 3 patients (30%); otherwise, grade 3/4 toxicities were limited.

Phase II assessment

Three phase II studies have further assessed the activity of radium-223 in the setting of mCRPC (**Table 1**). These studies differ slightly based on eligibility and treatment schema. The first study followed a randomized placebo controlled design and included 64 patients with mCRPC and either one painful bony lesion or multiple bony metastatic sites.²⁸ All patients received external beam radiation therapy (EBRT) to a metastatic site and then were randomized to receive 4 simultaneous treatments with radium-223 or saline. Two primary endpoints were evaluated in this experience: (1) change in bone ALP levels and (2) time to first skeletal-related event (SRE). The study met the first of these two primary endpoints, with a more significant decline in bone ALP levels with radium-223 (–65.6% vs +9.3%, $P < 0.0001$). Furthermore, there was a substantial (albeit statistically insignificant) difference in time to first SRE ($P = 0.065$). Notably, a follow-up report from this trial suggests a survival advantage with radium-223 (65 vs 46 weeks; $P = 0.056$), consistent with the subsequently noted phase III experience.²⁹

A separate phase II study assessed a total of 100 patients with mCRPC and painful bony metastases.³⁰ In contrast to the previous study design, patients did not receive concomitant EBRT. Rather, patients were randomized to receive a single dose of radium-223 at 1 of 4 dose levels (5, 25, 50 or 100 kBq kg⁻¹). The primary endpoint of the study was to characterize pain responses using two primary indices: (1) the visual analog scale (VAS) and (2) analgesic use. The study met its primary endpoint, with an increased pain response at higher dose levels of radium-223 observed as early as week 2 ($P = 0.035$). At week 8, the proportions of individuals with a decrease in pain and

Table 1: Phase II studies assessing radium-223 in mCRPC

Reference	Patient population	n	Details
Nilsson <i>et al.</i> ²⁸	mCRPC 1 painful bony lesion (or) Multiple bony metastases	64	Design All patients receive a single dose of EBRT Patients then receive 4 cycles of radium-223 or saline Primary endpoint (s) Change in bone ALP Time to first SRE Key result (s) Decline in bone ALP (−65.6% vs +9.3%, $P<0.0001$) Borderline improvement in time to first SRE (HR=1.75; 95% CI=0.96–3.14; $P=0.065$)
Nilsson <i>et al.</i> ³⁰	mCRPC Painful bony metastases	100	Design All patients received a single dose of radium-223 either 5, 25, 50, or 100 kBq/kg Primary endpoint (s) Pain response based on VAS and analgesic use Key result (s) Increased pain response at higher doses by week 2 ($P=0.035$) Dose response with respect to decrease in pain and analgesic use by week 8 ($P=0.040$)
Parker <i>et al.</i> ³¹	mCRPC Failed standard of care therapies	122	Design All patients received either 25, 50, or 80 kBq/kg of radium-223 every 6 weeks×3 Primary endpoint (s) PSA decline ($\geq 50\%$) Key result (s) Dose-dependent decline in PSA ($P=0.0297$) Decline in ALP at higher dose levels ($P<0.0001$)

mCRPC: metastatic castration-resistant prostate cancer; EBRT: external beam radiation therapy; ALP: alkaline phosphatase; SRE: skeletal-related event; CI: confidence interval; HR: hazard ratio; VAS: visual analog scale; PSA: prostate-specific antigen

stable analgesic use (at increasing dose levels) were 40%, 63%, 56% and 71%, respectively ($P=0.040$). As with the previous phase II experience, changes in markers of bone turnover seemed to be increased at higher dose levels, with a significant decrease amongst those patients treated at 100 kBq kg^{−1}.

The third and largest randomized phase II trial assessed 122 patients with mCRPC who had exhausted available therapeutic modalities.³¹ Whereas the previous two studies were designed to evaluate palliative endpoints (time to SRE, pain response, etc.), the current study was powered to evaluate the proportion of individuals who achieved a prostate-specific antigen (PSA) decline of $\geq 50\%$. Patients were randomized in a double-blind fashion to receive a total of three 6-weekly doses of radium-223 at 25, 50 or 80 kBq kg^{−1}. There appeared to be a dose response, with 0%, 6% and 13% of patients achieving a $\geq 50\%$ PSA decline in the respective cohorts ($P=0.0297$). Greater declines in ALP values were also seen in at higher dose levels, with a $\geq 50\%$ decline in just 16% of patients treated at 25 kBq kg^{−1}, when compared with 66% and 67% of patients treated at 50 and 80 kBq kg^{−1}, respectively.

Phase III assessment

In light of compelling phase II data, radium-223 was further explored in the phase III ALSYMPCA study.¹⁹ In this study, 921 patients with mCRPC were randomized in a 2:1 fashion to receive either 6 injections of radium-223 at 4 week intervals (dosed at 50 kBq kg^{−1}) or placebo, both in combination with best standard of care which was consisted of various secondary hormones. Key eligibility criteria in this study included symptomatic castration-resistant disease, ≥ 2 bone metastases and no visceral metastases. Importantly, patients must have either failed or refused docetaxel therapy, or been deemed unfit. Patients were stratified on the basis of baseline ALP, bisphosphonate use and receipt of prior docetaxel therapy.

The primary endpoint of the study was OS, with secondary endpoints including time to first SRE, time to ALP progression, response and normalization and time to PSA progression.¹⁹ Secondary endpoints also included assessment of safety and quality of life. Ultimately, with 541 patients randomized to receive radium-223 and 268 patients randomized to receive placebo, demographic features of both groups were similar. Median age on both study arms was approximately 70 and Caucasians comprised approximately 94% of patients enrolled. The majority of patients enrolled had multiple metastases, with roughly 40% of patients demonstrating > 20 metastases on baseline imaging. Just over half of the enrolled population (54%) had a World Health Organization cancer pain index ≥ 2 .

A pre-specified interim analysis of the primary endpoint was set to occur after 320 events.¹⁹ At the time of this interim analysis, a significant improvement in OS was noted with radium-223 as compared to placebo (14.0 months vs 11.1 months, HR = 70 and $P=0.00185$). An updated analysis of OS prior to randomization showed only slight differences in this comparison (14.9 vs 11.3; $P<0.001$). Several secondary endpoints were also markedly improved amongst patients receiving radium-223 – for instance, a significant delay in time to first symptomatic skeletal event (SSE) was noted (15.6 months vs 9.8 months, $P<0.001$). A further analysis of SSE suggested that the incidence of pathologic bone fractures, spinal cord compression and use of EBRT were all significantly delayed.³² Notably, this endpoint is unique amongst recent trials exploring therapy for mCRPC. Details related to delay in radiographic progression with radium-223 are not available at this time. Notably, published details of the study do not allude to any defined schedule of radiographic assessments, challenging interpretation of this endpoint. With respect to quality of life, a longitudinal assessment of the functional assessment of cancer therapy-prostate (FACT-P) questionnaire showed a larger improvement amongst those patients receiving radium-223 as compared to placebo (25% vs 16%, $P=0.02$). Furthermore, deterioration in ECOG PS (≥ 2 points) was less frequent in the subgroup receiving radium-223 as compared to placebo (HR = 0.62, 95% confidence interval (CI) 0.46–0.85; $P=0.003$).³³

Several biomarker assessments in the ALSYMPCA trial also deserve mention. Time to increase in ALP was significantly prolonged in patients receiving radium-223 (HR = 0.17; 95% CI 0.13–0.22; $P<0.001$).¹⁹ A recent detailed analysis of ALP data suggests that the ALP may have independent prognostic value for OS ($P<0.0001$).³⁴ Furthermore, a decline in ALP from baseline was seen more frequently with radium-223 as compared to placebo (87% vs 23%; $P<0.001$), suggesting that the trend in ALP may have predictive value, as well. Time to increase in PSA was also delayed in the radium-223 arm (HR = 0.64, 95% CI 0.54–0.77; $P<0.001$). However, details related to PSA response (i.e. the proportion of patients with a 30% or 50% decline in PSA) are not currently available.

Although several earlier experiences with radium-223 called particular attention to hematologic toxicities, few substantial differences between radium-223 and placebo were noted in the ALSYMPCA experience.¹⁹ For instance, the rates of all grade anemia were balanced (27% in both arms), as were the rates of grade 3/4 anemia (11% with radium-223 vs 12% with placebo). Rates of all grade neutropenia and thrombocytopenia were low, occurring in < 10% of patients enrolled on either treatment arm. Similarly, grade 3/4 neutropenia occurred in < 5% of patients in either group. With respect to non-hematologic toxicities, bone pain was noted in a lesser proportion of patients receiving radium-223 as compared to placebo (43% vs 58%), pointing toward the potential palliative benefit of the compound. An appreciable rate of all-grade diarrhea (22%), nausea (34%) and vomiting (17%) were seen with radium-223 (notably, these rates are higher than those seen with novel endocrine therapies, such as abiraterone and enzalutamide). However, fewer than 2% of patients experienced grade 3/4 events amongst these selected toxicities. With follow-up now extending to roughly 1.5 years after treatment, no new major toxicities have been observed.³⁵

Several more recent secondary analyses shed light on key questions related to the clinical application of radium-223. For instance, approximately 57% of patients enrolled had prior docetaxel exposure, while the remainders were docetaxel-naïve (deemed either unfit or refused treatment).³⁶ Importantly, the OS benefit was seen in both docetaxel pre-treated and non-docetaxel treated patients (HR = 0.71; 95% CI 0.56–0.89 and HR = 0.74; 95% CI 0.56–0.99, respectively). The median survival in the pre-docetaxel group was substantially in favor of radium (16.1 vs 11.5 months, $P = 0.039$). Rates of grade 3/4 neutropenia were higher in patients with prior docetaxel receipt, suggesting that myelosuppression from prior cytotoxic therapy may potentially augment hematologic toxicity from radium-223. Notably, a separate report also cited more extensive disease (>6 metastases) as a risk factor for anemia and a low ALP level as a risk factor for both anemia and thrombocytopenia.³⁷ A detailed analysis of pain related parameters also suggests the potential palliative benefit of radium-223.³⁸ Among the subset of patients with no baseline opioid use, there was a longer time to first opioid use among those patients receiving radium-223 (HR = 0.621; 95% CI 0.456–0.846). A lesser proportion of patients receiving radium-223 also required opioids for pain relief (36% vs 50%).

FUTURE DIRECTIONS

The compelling data for radium-223 ultimately led to approval of the agent on May 15, 2013.²⁰ Perhaps the biggest challenge for investigators will be to determine how to sequence and/or combine this therapy amongst other emerging options for mCRPC. There is a veritable game of musical chairs that is ongoing amongst therapies for the disease. For instance, the pivotal trial of sipuleucel-T was conducted in minimally symptomatic or asymptomatic mCRPC patients with largely chemotherapy-naïve disease – thus, it has primarily been envisioned for use in the pre-docetaxel space.⁹ On the other hand, agents such as enzalutamide and abiraterone originally gained their approval in the post-docetaxel space on the basis of phase III trials conducted this population.^{10,13} However, phase III data from pre-chemotherapy studies (COU-AA-302 and PREVAIL) have already put abiraterone and may soon put enzalutamide in the same territory.^{11,39} The net effect is to shift further back the use of docetaxel. With this phenomenon in mind, the use of radium-223 may potentially supersede docetaxel, especially in older patients, patients with multiple comorbidities and other subsets where cytotoxic chemotherapy may not be preferred. Limited clinical

evidence exists, however, to guide the use of radium-223 in patients with asymptomatic disease. Therefore, it is unlikely that radium-223 would be used prior to agents such as enzalutamide, abiraterone and sipuleucel-T – rather, it would likely be sequenced after these therapies, at the onset of symptoms. It should be noted that some overlap may exist between patients treated in the ALSYMPCA study and patients treated on other phase III trials for “asymptomatic” disease. The latter group of trials excluded patients who were taking narcotic medications, but patients may have been on agents such as ibuprofen or acetaminophen. Similar patients may have been enrolled on ALSYMPCA – as such, patients receiving non-narcotic pain medications may be candidates not just for novel endocrine and vaccine therapies, but for radium-223 as well.

Radium-223 was administered in combination with best standard of care in the ALSYMPCA trial (chemotherapy and other isotopes were excluded). Best standard of care included combination with a variety of hormonal agents such as estrogens, dexamethasone, ketoconazole and antiandrogens. Thus, it is logical to use radium-223 with a variety of hormonal therapies. It is important to recognize that in ALSYMPCA, radium-223 was never administered as a monotherapy. Though the use of radium-223 with newer hormones such as abiraterone and enzalutamide has not been tested in clinical trials, there is no reason to think that safety issues would be a problem. It is hard to argue that sequential therapy will provide optimal care to patients. Neuroendocrine phenotypes are likely to emerge which provide unique challenges.⁴⁰ Furthermore, limited data is available to document whether a substantial proportion of patients will maintain a functional status that allows for receipt of 4–5 lines of therapy for castration-resistant disease.

The clinical and commercial viability of radium-223 may necessitate utilization in earlier therapeutic settings. A phase I/II study is currently ongoing to assess the combination of radium-223 with docetaxel.³⁵ Preliminary data from the phase I component of this study indicates no long-term toxicities with the regimen to date and no discontinuation of radium-223 due to adverse events. Notably, 4 cases of febrile neutropenia were observed. The phase II component of the study is moving forward with a dose of docetaxel at 60 mg m⁻² every 3 weeks in combination with radium-223 at 50 kBq kg⁻¹ every 6 weeks. Recent interviews with experts in the field of prostate cancer suggest that there is a comfort level with administering radium-223 in combination with endocrine therapies, such as enzalutamide or abiraterone.⁴¹ Financial issues may come to the fore when combining pricey novel therapies for mCRPC. At US \$69 000 for a series of 6 treatments, radium-223 (on a monthly basis) is more expensive on a monthly basis than abiraterone and enzalutamide. In an evolving healthcare system with strained resources, dual therapies will present challenges.

If radium-223 were to move to the upfront setting in those with bone metastatic disease, would early use of a radiopharmaceutical potentially cause evolution of secondary malignancies? In the ALSYMPCA study, median survival was 14.9 months on the experimental arm.¹⁹ However, in the setting of hormone sensitive metastatic disease, median survival might well exceed 5 years based on recent reports, offering a greater opportunity for secondary malignancies to develop.⁴² An FDA mandate for further studies may provide valuable information in this regard (Table 2). In the FDA approval letter for radium-223, a total of 4 further studies were required.²⁰ The largest of these is a 1200 patient observational study that will assess the long-term safety of radium-223 in patients with castration-resistant prostate cancer and bone metastases.⁴³

The other mandated studies also address current gaps in knowledge related to radium-223. For instance, in the phase I studies cited herein,

Table 2: FDA mandated studies for radium-223²⁰

Study number	Patient population	Final protocol submission	Study completion	Details
2041-1	mCRPC Bone metastases	9/2013	12/2023	Observational study of 1200 patients Radium-223 dosed identically to ALSYMPCA study (50 kBq kg ⁻¹ every 4 weeks×6) Designed to address Risk of long-term bone marrow suppression Risk of developing secondary malignancies
2041-2	mCRPC Symptomatic bone metastases No visceral metastases	12/2013	12/2017	Randomized clinical trial Designed to address prospectively Risk of long-term bone marrow suppression Risk of developing secondary malignancies
2041-3	mCRPC Bone metastases	8/2013	9/2016	Prospectively assesses re-treatment with radium-223 Designed to address prospectively Risk of long-term bone marrow suppression Risk of developing secondary malignancies
2041-4	mCRPC Bone metastases	9/2013	9/2018	Will assess multiple dose levels of radium-223 above 50 kBq/kg Designed to address prospectively Utility of higher dose-levels of radium-223

FDA: food and drug administration; mCRPC: metastatic castration-resistant prostate cancer

doses up to 250 kBq kg⁻¹ appeared to be well tolerated – 5 times higher than the dose utilized in the ALSYMPCA trial.²⁶ A caveat to these datasets, however, is that only limited doses of radium-223 were administered. As such, a randomized phase II trial will be required to evaluate higher dose levels of radium-223, with the potential requirement for a phase III study to confirm encouraging findings.²⁰ Another mandated study will examine the feasibility and long-term safety of re-challenge with radium-223 – these studies will establish whether doses of radium-223 beyond the 6 cycles assessed in ALSYMPCA are feasible.

The future of radium-223 may also include a broader spectrum of diseases. As noted, the phase I studies included both patients with prostate cancer and breast cancer.²⁶ Mechanistically, there is little reason to think that the agent would be less effective across other disease types where bone metastases are frequently encountered. In contrast to vaccines and endocrine therapies for prostate cancer, there is no prostate-cancer specific tropism with radium-223. Radium-223 may potentially be effective in primary bone neoplasms; a phase I study is currently underway to explore the agent in high-risk osteosarcoma.³⁸

CONCLUSIONS

In summary, radium-223 represents a paradigm shift in the treatment of mCRPC. While radiopharmaceuticals were previously utilized solely for palliative benefit, the clinical benefit yielded from radium-223 places the agent alongside a growing list of endocrine therapies,

vaccines and cytotoxic therapies that have shown an improvement in OS. Given this growing list, the sequencing and various combinations of radium-223 will be a key issue in the coming years. In addition, FDA mandated studies may provide insights into potential long-term toxicities associated with the drug and may potentially unveil the utility of higher dose-levels or re-treatment. Ultimately, given the cost of radium-223 and other treatments for mCRPC, pharmacoeconomics may play an increasing role in how mCRPC therapies are rendered.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the conception, design, background research, writing and editing of this manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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